

REMARKS

A. Status of the Claims

Claims 1-7 were pending at the issuance of the instant Office Action. Claims 1-7 are rejected in the instant Office Action. No claims are amended, added, or canceled herein. Applicants thank the Examiner for the previous consideration of our submissions.

B. Rejections under 35 U.S.C. § 103(a)

Claims 1-7 stand rejected under 35 U.S.C. 103 as being obvious over Malfroy-Camine *et al.* (6,064,188) in view of LaHaye *et al.* (5,075,116), Crapo *et al.* (5,994,339), Campbell *et al.* (6,177,419), and Winkler *et al.* (Molecular Vision 1999).

The present invention is directed to the use of certain superoxide dismutase mimics to treat persons suffering from AMD, diabetic retinopathy, or retinal edema. MPEP §2143.03 requires that all claim limitations be considered in an obviousness determination, and the Board of Patent Appeal and Interferences (BPAI) recently confirmed that “obviousness requires a suggestion of all limitations in a claim.” See *In re Wada and Murphy*, Appeal 2007-3733, citing *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Circ. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). Applicants submit that none of the cited art teaches or suggests the use of the compounds in the instant claims to treat AMD, diabetic retinopathy, or retinal edema. In particular, it is submitted that Crapo, *et al.*, LaHaye *et al.*, Campbell *et al.*, and Winkler *et al.* fail to cure the conceded deficiency in Malfroy-Camine *et al.*, and that the asserted combination of Malfroy-Camine *et al.*, LaHaye *et al.*, Campbell *et al.*, Crapo *et al.*, and Winkler *et al.* therefore fails to render the instant claims obvious.

The Action concedes that Malfroy-Camine *et al.* do not teach or suggest the use of the compounds in the instant claims for the treatment of AMD, diabetic retinopathy, or retinal edema (see page 2 of the Office Action mailed 11/17/04). Nevertheless, the Action rejects the instant claims, asserting that LaHaye *et al.*, Campbell *et al.*, Crapo *et al.* and Winkler *et al.* provide the necessary disclosure. In particular, the Action asserts that LaHaye *et al.* teach the use of free radical scavengers and antioxidants for treating macular degeneration (see page 3 of the Office Action mailed 10/19/07), that Winkler *et al.* teach the role of oxidation in macular degeneration and the use of superoxide dismutase to prevent oxidative damage (see page 3 of the Office

Action mailed 10/19/07), that Campbell *et al.* teach the use of the claimed compounds in a pharmaceutical composition that can be administered by injection (see page 3 of the Office Action mailed 10/19/07), and that Crapo *et al.* teach the use of compounds having superoxide dismutase activity for the treatment of macular degeneration (see page 3 of the Office Action mailed 10/19/07). Applicants respectfully traverse this contention.

The Action's obviousness rejection appears to be based primarily on the reasoning that LaHaye *et al.* and Crapo *et al.* and Winkler *et al.* teach a general concept that superoxide dismutase compounds can be used to treat macular degeneration. Applicants submit that the combination of references is inadequate to support the Action's reasoning. As discussed below, these references do not teach or suggest that any superoxide dismutase compound can be used to treat macular degeneration, diabetic retinopathy, or retinal edema.¹

The Action appears to oversimplify the teaching of LaHaye *et al.*, which relates to the use of small vitamin antioxidants, an amino acid (L-cysteine), and cofactors (such as zinc, copper, selenium, and manganese) for metalloenzymes. Specifically, the Action asserts that LaHaye *et al.* teach that free radical scavengers and antioxidants can be used to treat macular degeneration, but fails to mention that LaHaye *et al.* actually teach a combination therapy that involves a plurality of antioxidants, a plurality of cofactors, and one or more glutathione-elevating compounds. LaHaye *et al.* do not teach or suggest that any one of these components of the therapy would be useful by itself to treat macular degeneration. Further, the combination therapy taught by LaHaye *et al.* does not include superoxide dismutase mimics. Thus, the teaching of LaHaye *et al.* would not have motivated one of skill in the art to use superoxide dismutase compounds for treating macular degeneration, diabetic retinopathy, or retinal edema.

The Action continues to rely on Crapo *et al.* as allegedly teaching compounds structurally similar to the compounds of the instant claims, and allegedly standing for the proposition that *any* superoxide dismutase can be used to treat macular degeneration (see, for example, page 3 of the Office Action mailed 10/19/07). However, Applicants submit that the Action's reliance on the teaching of Crapo *et al.* is inappropriate for at least the following two reasons: the teaching of Crapo *et al.* relates to compounds that are structurally dissimilar to the compounds of the instant

¹ Crapo *et al.* suggest that certain porphyrin-containing compounds may be useful for protecting against the damage caused by macular degeneration, but do not teach or suggest that the compounds would be useful for treating macular degeneration

claims, and Crapo *et al.* do not teach that such compounds can be used to treat macular degeneration. In particular, the compounds taught by Crapo *et al.* are specifically porphyrin-containing compounds, while the compounds of the instant claims are specifically salen-metal complexes. Therefore, the compounds taught by Crapo *et al.* are not structurally similar to the compounds of the instant claims. Also, Crapo *et al.* do not teach or suggest the aforementioned broad proposition asserted by the Action. Indeed, at column 16, line 58-60, Crapo *et al.* suggest that the particular mimetics of the invention can be used to *protect against the damage caused by* macular degeneration, as opposed to actually treating macular degeneration (emphasis added).

Applicants also submit that the teaching of Winkler *et al.* fails to cure the deficiencies of Malfroy-Camine *et al.*, LaHaye *et al.*, and Crapo *et al.* The Action asserts that Winkler *et al.* teach the role of oxidation in relation to macular degeneration and the effect of superoxide dismutase in preventing oxidative damage caused by macular degeneration (see page 3 of the Office Action mailed 10/19/07). Applicants submit that the Action has mischaracterized the teaching of Winkler *et al.*, and erroneously relies upon the reference in arriving at the instant invention.

The Winkler reference is a review article that discusses “the *potential* role of oxidation in relation to age-related macular degeneration” (see Abstract of Winkler, emphasis added). The Action concedes that Winkler *et al.* do not provide any data to support the proposition that superoxide dismutase could be used to treat AMD, but contends that “the mere suggestion that superoxide dismutase protects against macular degeneration makes such reference a valid reference” (see page 4 of the Office Action mailed 10/19/07). However, the alleged suggestion by Winkler *et al.* is diminished by the confession that “it remains unclear whether oxidation is a causative factor in the progression of AMD” (see second column, second page of Winkler). Furthermore, Winkler *et al.* focus the majority of their discussion on studies involving non-enzyme antioxidants including glutathione (GSH), vitamin C, vitamin E, and carotenoids. Superoxide dismutase is mentioned as only one of many oxidants. Since the teaching of Winkler *et al.* is not focused on superoxide dismutase, and fails to elaborate on the possible role of superoxide dismutase in the discussion of oxidants that may (or may not) be involved in AMD progression, Applicants submit that more than the mere suggestion referred to by the Action is needed to motivate one of skill in the art to consider using the particular compounds of the instant claims to treat AMD.

Furthermore, as stated in MPEP 2143.02(II), “obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness” (citing *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)). Applicants have provided evidence that there was no reasonable expectation of success for using superoxide dismutase compounds to treat AMD, diabetic retinopathy, and/or retinal edema based on the teaching of Winkler *et al.* or based on the knowledge of one skilled in the art at the time the instant application was filed.² However, Applicants submit that the Action has mischaracterized the evidence of record.

The Action states that “applicant in his remarks admits that both articles (referring to De La Paz and Delcourt) show the oxidative mechanism may play a role in the development of AMD” (instant Office Action, page 2). However, the Action appears to mischaracterize Applicants’ remarks relative to the teachings of these references. There are numerous oxidative mechanisms (not one, as implied by the quote from the Action mentioned above) involving a large universe of oxidative compounds, including numerous oxidative enzymes and antioxidants. De La Paz and Delcourt do not narrow the universe to superoxide dismutases. On the contrary, these references teach away from such a narrowing by concluding that there is no significant association between disease severity of AMD and superoxide dismutase activity, and that high levels of erythrocyte superoxide dismutase activity were not associated with late AMD and early signs of AMD (see discussion on pages 3 and 4 of Applicants’ Response submitted April 8, 2008).

MPEP §2143.02 (II) states that “the test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teaching of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another.” In view of the totality of the art at the time the instant application was filed, there was no expectation of success for the use of superoxide

² Applicants presented evidence in the form of the teachings of De La Paz and Delcourt, which were discussed in Applicants’ Response submitted August 1, 2007 and in Applicants’ Response submitted April 8, 2008

dismutase compounds to treat AMD based on Winkler *et al.* or any of the other references cited by the Action.

Also, the Action indicates that Campbell *et al.* was cited simply to demonstrate that injection is a routine route of ophthalmic delivery (page 5, Office Action mailed 10/19/07). Campbell *et al.* teach ophthalmic administration of bipyridine manganese complexes, which are not even remotely related to the compounds of the instant claims (contrary to the allegation of the Action as stated in the Office Action mailed 10/19/07, page 3). The Action concedes that the compounds of Campbell *et al.* are not taught for the treatment of disorders such as macular degeneration (Office Action mailed 10/19/07, page 3). Nonetheless, the Action contends that one of skill in the art would have been motivated to administer compounds mentioned in the instant claims by injection to the eye based on Campbell *et al.* Applicants submit that the allegation is not supported by the other references cited in the aforementioned combination, because the combination as a whole does not teach the use of compounds with superoxide dismutase activity to treat macular degeneration, diabetic retinopathy, or retinal edema.

In addition, the universe of compounds that may be involved in oxidative mechanisms is very large. The Federal Circuit in *Eisai Co. v. Dr. Reddy's Labs* indicated that “the Supreme Court’s analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a ‘finite number of identified, predictable solutions.’” (*Eisai Co. v. Dr. Reddy's Labs, Ltd.*, 487 USPQ2d 1452 (Fed. Cir. 2008) citing *KSR Int’l Co. v. Teleflex*, 127 S. Ct. at 1742. The Supreme Court in *KSR Int’l v. Teleflex Inc.* stated that “there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR Int’l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). Here, there is no articulated reasoning with some rational underpinning to support the legal conclusion of obviousness, and the Action has not pointed out any reasons based on the aforementioned relied upon references or anything else that would have motivated one of skill in the art to select the compounds of the instant invention out of the vast universe of oxidant scavengers and antioxidants to treat macular degeneration, diabetic retinopathy, or retinal edema. The teachings of the relied upon references are not sufficient to support the Action’s conclusion that it would have been obvious to use any superoxide dismutase compounds to treat macular degeneration, diabetic retinopathy, or retinal edema.

In light of the foregoing arguments, Applicants submit that the Action has erred in combining the cited references to arrive at the instant invention. Consequently, Applicants respectfully request that the obviousness rejection be withdrawn.

Conclusion

This is submitted to be a complete response to the outstanding Action. The Examiner is invited to contact the undersigned attorney at (817) 615-5330 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

/Jason J. Derry, #50,692/

Jason J. Derry, Ph.D.

Reg. No. 50,692

Attorney for Applicants

ALCON RESEARCH, LTD.
6201 S. Freeway, Q-148
Fort Worth, TX 76134-2099
(817) 615-5330

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